Original Article

Carotid intima media thickness in type 2 diabetes mellitus with ischemic stroke

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ABSTRACT

Background: Diabetes mellitus is associated with high cardiovascular risk. Carotid intima media thickness (CIMT) is used commonly as a noninvasive test for the assessment of degree of atherosclerosis. The objective of this study was to find out the cut-off point for CIMT for ischemic stroke in patients with type 2 diabetes mellitus (T2DM) and to correlate CIMT with various parameters like smoking, hypertension, lipid profile and duration of T2DM. **Materials and Methods:** A total of 80 subjects in the age group of 30–75 years (M:F = 57:23) were selected and divided into three groups, i.e. diabetes with ischemic stroke, diabetes and healthy subjects. All the participants were subjected to B-mode ultrasonography of both common carotid arteries to determine CIMT, along with history taking, physical examination and routine laboratory investigations including included fasting and 2-hour postprandial blood sugar, blood urea, serum creatinine, lipid profile, glycated hemoglobin, and microalbuminuria. **Results:** Patients with T2DM with or without ischemic stroke were found to have significantly higher prevalence of increased CIMT and a value greater than 0.8 mm was found to be associated with the occurrence of stroke. The mean carotid IMT of the group as a whole was 0.840 ± 0.2 mm. The mean carotid IMT was not significantly different between T2DM patients with or without ischemic stroke (1.06 ± 0.2 vs. 0.97 ± 0.26 mm, $P = 0.08$). However, the mean CIMT was significantly higher in diabetic subjects compared to healthy subjects (1.01 ± 0.28 mm vs. 0.73 ± 0.08, $P = 0.006$). Other parameters like higher age, smoking, hypertension, hyperlipidemia, low HDL cholesterol, the glycemic parameters and the duration of diabetes were independently and significantly related to CIMT. **Conclusion:** A high CIMT is a surrogate and reliable marker of higher risk of ischemic stroke amongst type 2 diabetic patients. Our study demonstrates the utility of carotid IMT as a simple non-invasive screening test for the assessment of atherosclerosis risk/prognosis in type 2 diabetics.

Key words: B-mode ultrasonography, carotid intima media thickness, diabetes mellitus, ischemic stroke

Introduction

Cardiovascular diseases are the most common cause of mortality in patients with type 2 diabetes mellitus (T2DM).[1] The Framingham study and the Multiple Risk Factor Intervention Trial (MRFIT) showed a 2–3 fold elevation in the risk of clinically evident atherosclerotic disease in patients with T2DM.[2,3] Similarly, Insulin Resistance Atherosclerotic Study (IRAS) has shown progression of atherosclerosis in persons with T2DM.[4] The Cholesterol Lowering Atherosclerosis Study (CLAS) has attributed this heightened risk to atherogenic profile associated with T2DM.[5]

World Health Organization has defined stroke as the rapidly developing clinical signs of focal/global disturbances of cerebral function, with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of

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vascular origin.[6] Stroke is the commonest life-threatening neurological disease and is the third most common cause of death surpassed only by cardiovascular disease and cancer.

Stroke is of two types: (i) ischemic 80–85% and (ii) hemorrhagic 15–20%.[7] Ischemic strokes are further divided into (a) thrombotic (b) embolic and (c) secondary to systemic hypoperfusion. Apart from other risk factors like hypertension, smoking, hyperlipidemia, family history of coronary artery disease (CAD), etc., diabetes mellitus is a well-recognized risk factor of coronary and cerebrovascular diseases.[7-9]

Carotid intima media thickness (CIMT) is widely used as a measure of atherosclerosis, considered to be an important pathogenic mechanism of thrombotic stroke.[10] Increased CIMT is associated with a higher prevalence of CAD and correlates with future development of myocardial infarction and stroke.[11] Atherosclerosis Risk In Community (ARIC) study reported that when compared with internal carotid artery, IMT of common carotid artery (CCA) was found to be a stronger marker of future stroke.[12] The B-mode ultrasonography is widely recommended for evaluation of CIMT.[13] To our sincere belief, this is the first such study on Indian diabetic patients with ischemic stroke.

Materials and Methods

The present work was undertaken in collaboration between Department of Endocrinology, Medicine and Radiology, Medwin Hospitals, Hyderabad, during the period May 2009 to May 2011. After approval by ethical committee, due consents were taken from the respective patients and guardians of the patients in the event of stroke.

The patients were divided into three groups:

Group A: Patients of either sex in the age group of 30–75 years with T2DM with or without hypertension with ischemic stroke demonstrated on CT scan.

Group B: Age-matched T2DM patients of either sex without any prior history of transient ischemic attack or stroke.

Group C: Age-matched normal individuals of either sex.

The following groups of diabetic patients with stroke were excluded from our study:

1. cardioembolic stroke,
2. patients with hemorrhagic stroke, and
3. patients with stroke due to secondary causes like trauma, impaired coagulation or tumor.

Subjects under group B and C were selected from outpatient clinics of endocrinology and medicine departments. A thorough medical history including duration of diabetes, history of hypertension, smoking, and alcohol intake was obtained. All patients were subjected to complete physical examination followed by an array of investigations including routine hemogram, complete urine examination, urine for microalbuminuria, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), glycated hemoglobin (HbA1C), lipid profile, renal and liver function tests, electrocardiography, computed tomography of brain and high-resolution B-mode ultrasonography for CIMT measurement. Subjects under group A were admitted to the inpatient department for evaluation.

Trained sonographers performed the B-mode ultrasound examination with a linear array transducer of 7.5–12 MHz on the selected subjects in supine position with the head slightly extended and turned to the opposite direction of the CCA being studied. Both sides were imaged at three places, i.e. at the proximal part, mid part and the bulb. The means of the three maximum right and three maximum left far wall measurements were calculated for each CCA. In our study, all the six right and left wall values were measured and the average values noted.

On a longitudinal, two-dimensional ultrasound image of CCA, each anterior (near) and posterior (far) wall of the CCA were displayed as two bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line (the blood–intima interface) of the far wall and the leading edge of the second bright line (media–adventitia interface) indicates the IMT [Figure 1].[14] A reading of more than 0.8 mm is considered to be abnormal and taken as the earliest marker of atherosclerosis.[15]

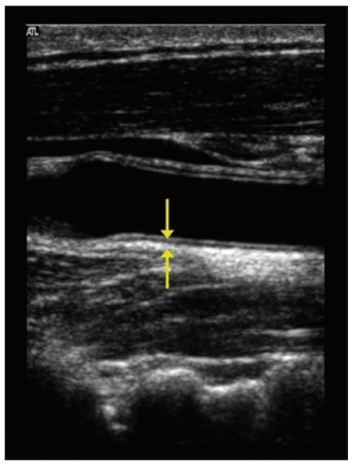

Figure 1: Measurement of carotid intima media thickness: The distance between the leading edge of the first bright line (the blood–intima interface) of the far wall and the leading edge of the second bright line (media–adventitia interface) indicates the IMT

Classification of plaques was done as per the following:[16]

Type I: Thin rim over the surface, but predominantly anechoic
Type II: <25% echogenic components
Type III: <25% hypoechoic components
Type IV: Predominantly echogenic

Objectives of the study were:

1. to find out the cut-off point for CIMT for ischemic stoke and
2. to correlate CIMT with various parameters like smoking, hypertension, lipid profile and duration of T2DM.

Statistical analysis

Online Graphpad Quickcalcs software (Graphpad Software Inc, La Jolla, CA, USA, available at http://www.graphpad.com/quickcalcs/index.cfm) was used for statistical calculations. Continuous data were analyzed by student's *t*-test. The categorical data were analyzed by using two-tailed Fisher's exact test. *P* values less than 0.05 were considered significant. Analysis of variance (ANOVA) was used to find the correlation between the CIMT and different variables.

Results

Forty patients (M:F = 30:10) were selected in group A with a mean age of 60.4 ± 10.2 years (range: 40–75 years). Twenty patients (M:F = 12: 8) were selected in group B with a mean age of 56.8 ± 11.7 years (range: 35–72 years) and 20 subjects (M:F = 15:5) were selected in group C with a mean age of 51.3 ± 16.7 years (range: 30–67 years). Of the total patients, 57 patients were males (71.4%) and 23 were females (28.6%). Majority of these subjects (25–31.3%) were distributed in the age group of 61–70 years, of whom 19 were males (76%) and 6 were females (24%).

Table 1 outlines the findings of B-mode ultrasonography and the CIMT values in subjects under different groups. The mean CIMT of the group as a whole was 0.85 ± 0. 3 mm. The mean CIMT of the diabetic patients (combined group A and C) was 1.01 ± 0.28 mm. Thirty-seven patients from group A (92.5%, M:F= 30:7), 16 subjects from group B (80%, M:F = 12:6) and 4 subjects from group C (20%, M:F = 3:1) had CIMT >0.8 mm. Out of total 80 study subjects, 57 (71.3%) were found to have increased CIMT (>0.8 mm), of whom 45 were males (78.9%) and 12 were females (21.1%). The difference in CIMT between patients under group A (1.06 ± 0.2) and group B (0.97 ± 0.26) was not significant (*P* = 0.08). However, CIMT in group A and group B subjects versus group C subjects was significant (group A vs. group C, *P* = 0.003; group B vs. group C, *P* = 0.03; combined group A and B vs. group C, *P* = 0.006). Figure 2 outlines the male versus female distribution of increased CIMT in the different subgroups.

Table 2 depicts the distribution of increased CIMT across different age sex brackets and body mass index (BMI). Five subjects out of total 22 subjects with BMI <25 kg/m^2 (6.3%), 44 out of 50 subjects with BMI 25–30 kg/m^2 (88%) and 8 out of 8 subjects with BMI >30 kg/m^2 (100%) had CIMT of >0.8 mm. Figure 3 depicts the distribution of increased CIMT in relation to duration of diabetes, hypertension, smoking and alcohol. Fifteen out of 16 (93.8%) patients with duration of T2DM >10 years had CIMT >0.8 mm versus 38 out of 44 (86.4%, *P* = 0.07) patients with duration of T2DM <10 years. Similarly, 34 patients out of total 37 hypertensive patients (91.9%) had CIMT >0.8 mm versus 23 of 43 non-hypertensive patients (53.5%, *P* = 0.004). Out of 27 smokers, 26 patients (96.3%) had CIMT >0.8 mm in contrast to 31 patients out of 53 nonsmoker subjects having CIMT >0.8 mm (58.5%, *P* < 0.0001). Finally, 17 subjects of the total 18 alcoholics (94.44%) had CIMT >0.8 mm in contrast to 40 patients out of 62 nonalcoholic patients (64.5%, *P* = 0.06).

Table 3 depicts the correlation of lipid profile and glycemic

Table 1: Carotid intima media thickness values determined by B-mode ultrasonography in subjects under different groups

Parameters	Right CIMT (mm)			Left CIMT (mm)			Average (mm)
Groups	Proximal	Mid	Bulb	Proximal	Mid	Bulb	
Group A	0.95± 0.17	0.94± 0.19	1.17± 0.35	1.0± 0.22	1.03± 0.28	1.25± 0.51	1.06± 0.2
Group B	1.01± 0.19	0.88± 0.14	0.98± 0.44	0.98± 0.16	0.94± 0.25	1.07± 0.68	0.97± 0.26
Group C	0.78±0.1	0.73±0.11	0.71± 0.11	0.77± 0.11	0.71± 0.1	0.69± 0.09	0.73± 0.08

	Number of patients with CIMT in mm			
	≤0.8 (%)	>0.8-1.2 (%)	> 1.2-1.5 (%)	> 1.5 (%)
Group A (n=40)	3 (7.5)	30 (75)	7 (17.5)	0 (0)
Group B (n= 20)	4 (20)	14 (70)	1 (5)	1 (5)
Group C (n= 20)	16 (80)	4 (20)	0 (0)	0 (0)

CIMT: Carotid intima media thickness

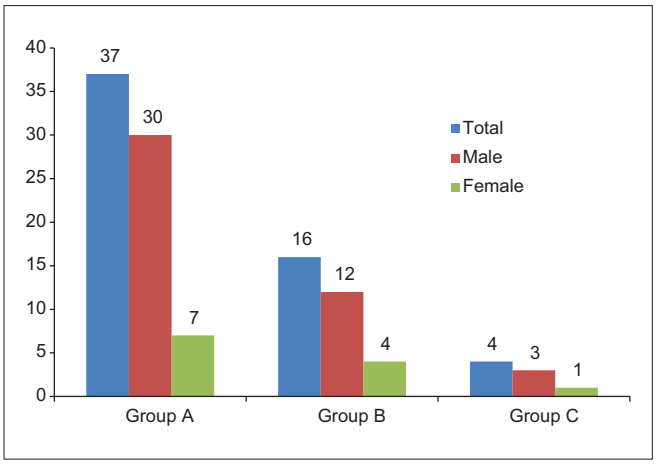

Figure 2: Increased carotid intima media thickness (>0.8 mm) in subjects under different groups

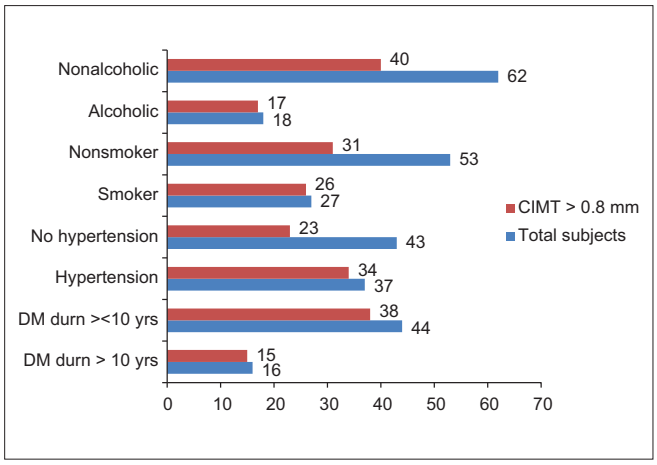

Figure 3: Distribution of increased carotid intima media thickness in relation to duration of diabetes, hypertension, smoking and alcohol

Table 2: Distribution of increased carotid intima media thickness across different age sex brackets and body mass index

BMI (kg/m²)	Total no of subjects		No of subjects with increased CIMT (>0.8 mm)	
	N=80	100%	N=57	71.3 %
< 25	22	27.5	5	6.3
25-30	50	62.5	44	55
>30	8	10	8	10
	Males (n=57)		Females (n= 23)	
Age Group (In years)	Number of subjects	Increased CIMT (>0.8 mm)	Number of subjects	Increased CIMT (>0.8 mm)
30-40 yrs	5	2	7	0
(n= 12)	8.77	3.51	30.43	0
41-50 yrs	7	4	3	2
(n=10)	12.28	7.01	13.04	8.69
51-60 yrs	16	13	6	3
(n=22)	28.07	22.8	26.08	13.04
61-70 yrs	19	16	6	6
(n=25)	33.33	28.06	26.08	26.08
71-75 yrs	10	10	1	1
(n= 11)	17.54	17.54	4.34	4.34
Total	57	45	23	12
(n=80)	100	78.9	100	52.1

Figures in parentheses are in percentage, CIMT: Carotid intima media thickness

Table 3: Correlation of lipid profile and glycemic parameters with relation to increased carotid intima media thickness

		CIMT < 0.8 mm	CIMT > 0.8 mm	*P* value
Lipid profile	Total Cholesterol (mg/dl)	166.2± 23.5	220.1± 34.3	0.0001
	LDL cholesterol (mg/dl)	94.1 ±15.8	139.8 ± 23.9	0.0001
	HDL cholesterol (mg/dl)	41.7± 8.3	30.5± 7.3	0.032
	VLDL cholesterol (mg/dl)	30.5 ± 7.2	41.7±8.6	0.078
	Triglyceride (mg/dl)	152.5± 19.6	208.7±23.6	0.0043
Glycemic profile	HbA1C	7.3 ± 2.5	8.9± 3.1	0.0001
	FBS (mg/dl)	132.5 ± 25.6	168.5± 31.5	0.0001
	PLBS (mg/dl)	175.6± 35.6	236.5± 42.7	0.0001

CIMT: Carotid intima media thickness, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low density lipoprotein, FBS: Fasting blood sugar, PLBS: Post-lunch blood sugar

parameters with relation to increased CIMT. Table 4 compares group A subjects in relation to total number of patients in terms of 0.1-mm CIMT increment. Out of the total 80 cases, 24 (30%) had CCA plaques. Twenty were from group A (83.3%), 4 from group B (16.7%) and none were from group C. Out of total 20 cases of ischemic stroke with CCA plaques, 10 had type 1 (50%), 5 had type II (25%), 2 had type III (10%) and 3 had type IV plaques (15%). Five cases from group A (12.5%), four cases from group B (20%) and five cases from group C (25%) were found to have plaque calcification, amounting to a total of 14 cases (17.5%), out of which 11 (78.6%) were males and 3 (21.4%) were females. Majority of the cases were found in the age group of 61–70 years. Table 5 shows the correlation between CIMT and different continuous variables.

Discussion

Ultrasonographic measurements of CIMT compared with histologic measurements at the far wall have been found to provide an accurate estimation of the IMT.[17] Agarwal *et al.* found a higher CIMT in diabetics who had CAD, even when the CAD was not clinically overt, leading to the conclusion that CIMT is a reliable surrogate marker for subclinical CAD in diabetic patients.[18] They found the CIMT in the overall study group to be 0.840 ± 0.2 mm, which is quite similar to the CIMT of our study group (0.85 ± 0. 3 mm). In our study, we found a 92.5% prevalence

Table 4: Comparison the group A subjects in relation to total number of patients in terms of 0.1 mm carotid intima media thickness increment

CIMT in subgroups (mm)	Total number of subjects		T2DM with ischemic stroke	
	N=80	% age	N=40	% age
≤ 0.8	23	28.75	3	13.04
>0.8-0.9	19	23.75	8	42.1*
>0.9-1.0	11	13.75	7	63.6*
>1.0-1.1	11	13.75	9	81.8*
>1.1-1.2	6	7.5	6	100*
>1.2-1.3	2	2.5	1	50*
>1.3-1.4	5	6.25	4	80*
>1.4-1.5	2	2.5	2	100*
>1.5	1	1.25	0	0

*P- 0.05, CIMT: Carotid intima media thickness

Table 5: correlation between the carotid intima media thickness and different continuous variables

Parameters	Correlation Coefficient	T value	*P* value
Age	0.493	5.009	< 0.0001
Duration of diabetes	0.484	4.884	< 0.0001
Systolic blood pressure	0.480	4.831	< 0.0001
Diastolic blood pressure	0.418	4.069	< 0.0001
Total cholesterol	0.478	4.810	< 0.0001
Triglyceride	0.270	2.481	0.015
LDL-cholessterol	0.481	4.844	< 0.0001
HDL-cholesterol	-0.190	-1.706	0.092
Fasting plasma glucose	0.399	3.841	< 0.0001
Post prandial glucose	0.482	4.841	< 0.0001
HbA1C	0.421	4.095	< 0.0001
Microalbuminuria	0.451	4. 754	<0.0001

LDL: Low-density lipoprotein, HDL: High-density lipoprotein,

of high CIMT in T2DM patients with ischemic stroke, 80% prevalence in T2DM patients without any stroke and 20% prevalence in nondiabetics. These prevalence rates vary as per the accompanying risk factors. The difference in occurrence of increased CIMT between group A and group B was statistically insignificant ($P = 0.08$), suggesting that both the groups are in almost the same risk. But the difference in CIMT between group A vs C, between group B vs C, and between combined group A & B versus group C was statistically significant ($P < 0.05$).

A study by Gupta *et al.* found tobacco use, obesity, high blood pressure, high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, and diabetes to correlate with vascular events.[19] As per the ultrasonographic measurements, it was observed that among patients with increased CIMT (>0.8 mm), male: female ratio was 3.75:1, suggesting that males are more vulnerable to have increased CIMT. This ratio was 4.3:1 in group A, 2:1 in group B and 3:1 in group C. So, males across the spectrum are more prone for high CIMT. As the age and BMI progresses, the risk of having increased CIMT goes up [Table 2]. In all age groups, males scored over females in having increased CIMT. Smokers had statistically significant higher prevalence of having increased CIMT (96.3% vs. 58.5%, $P = 0.004$). Though alcoholics had higher chances of having increased CIMT, this was not statistically significant ($P = 0.067$).

Hypertensive patients had significantly higher chances of getting increased CIMT than nonhypertensives. But though the subjects with duration of T2DM >10 years had a higher prevalence of increased CIMT, it was statistically not significant in comparison to subjects with duration of T2DM <10 years. Jadhav *et al.*,[20] in their study on the association of microalbuminuria with CIMT and CAD, observed that microalbuminuria had a strong association with high CIMT in diabetic subjects. Our results in diabetics are similar to their observations, as microalbuminuria had a significant correlation ($P < 0.0001$) with CIMT in this subgroup.

The ARIC study on 15,792 individuals aged 45–64 years reported statistically significant associations of change in CIMT with baseline diabetes, current smoking, HDL cholesterol, pulse pressure during follow-up from 1987 to 1998.[21] Jangrozik *et al.* concluded that stroke risk increases by 150–400% in people with T2DM.[22] The three glycemic parameters (FPG, PPPG, and HbA1C) and the lipid parameters like total cholesterol, LDL cholesterol, and triglyceride were all significantly higher in patients with increased CIMT. Though HDL cholesterol had a negative association with the occurrence of increased CIMT, it was not significant. A Finnish study has shown an association between LDL cholesterol and CIMT.[23] In a Muscatine study, a risk factor load model showed an inverse relation between HDL cholesterol and CIMT.[24]

Atherosclerosis, especially carotid atherosclerosis, plaque is a known cause of stroke.[10] Prevalence of plaque was higher in Group A than group B (83.3% vs. 16.7%). So, subjects with a plaque in CCA are more prone to develop ischemic stroke. Type I variety was the most common among subjects with T2DM and ischemic stroke. Increasing age and male gender is also significantly associated with plaque calcification. Saha *et al.* have demonstrated significant association between age, high-sensitivity C-reactive protein (hsCRP) and fibrinogen levels and high CIMT in patients with ischemic stroke.[25] We did not subject any of our patients to any of these novel risk factors.

Rotterdam study showed that increasing CIMT is a risk factor for stroke, analogous to coronary plaques in acute myocardial infarction.[26] CIMT in healthy middle-aged

adults measures 0.6–0.7 mm, and CIMT greater than 1.2 mm is considered abnormal.[27] CIMT is age dependent and increases at a rate of 0.005–0.010 mm/year.[28] Thus, in younger individuals, a CIMT of greater than 1.00 mm would be considered abnormal.[29] Table 4 shows that by comparing the group A cases (T2DM with ischemic stroke) and distributing them as per 0.1-mm increment of CIMT from 0.8 mm, it was observed that the incidence of ischemic stroke progressively increased significantly and attained 100% incidence on reaching a CIMT of 1.1–1.2 mm. Hence, we conclude that any increase in CIMT more than 0.8 mm adds to the risk of development of ischemic stroke. It can act as a surrogate marker of atherosclerosis and can be used as a routine screening tool.[30]

During the statistical calculation by linear regression (ANOVA), we also found that the variables like age, duration of diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, LDL cholesterol, FPG, PPPG and HbA1C significantly and positively correlated with CIMT, but HDL cholesterol had a negative correlation with the latter. Thus, routine measurement of CIMT may add value to risk stratification and facilitate better use of various treatment strategies in people with diabetes.[31] A recent study has suggested that max-IMT might be closely associated with the extent of coronary stenosis in type 2 diabetic patients without history of CAD but with carotid atherosclerosis.[32] However, data regarding CIMT as a marker for ischemic stroke in T2DM subjects are very limited. Our study would go a long way in providing insights into the utility of CIMT in diabetic subjects at risk for the development of stroke.

The limitations of our study are an overall small sample size, comparison of 60 diabetic versus 20 healthy subjects, single-center data, and operator variability in CIMT measurement. Also, the manual measurement techniques used in this study are inferior to the automated software-based methods of IMT measurement, which can simultaneously take multiple measurements. Nevertheless, data from the present study substantiate the earlier findings and add value to the limited information available on CIMT as a marker of ischemic stroke in diabetic patients.

In conclusion, we have demonstrated that increased thickness of the intima media layer of the common carotid arteries correlate well with ischemic stroke in the setting of T2DM, and the cut-off point for CIMT was determined by us to be 0.8 mm for the occurrence of ischemic stroke, which reaffirms the earlier findings. People with diabetes have higher CIMT than the healthy population. Furthermore, we have simultaneously elaborated that aging, smoking, hypertension, hyperlipidemia, low HDL cholesterol and the glycemic parameters and the duration of diabetes are independently and significantly related to CIMT. Hereby, we conclude that CIMT can be used as a valuable routine screening tool for the evaluation of atherosclerosis in T2DM patients. Our preliminary study paves way for further randomized studies including large number of patients from multiple centers with longer follow-up, which would assess the role of CIMT in predicting the development of various complications and how the various available treatment strategies could be incorporated to influence the outcome.

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